Accelerating adjuvant breast irradiation in women over 65 years: Matched case analysis comparing a 5-fractions schedule with 15 fractions in early and locally advanced breast cancer

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1. Introduction

The role of radiotherapy in the treatment of breast cancer has been established by multiple randomized trials, brought together in the meta-analyses of the Early Breast Cancer Trialists’ Collaborative Group [1]. The benefit of radiotherapy depends on the tumour recurrence risk, but even in the very favourable early stage breast cancer, radiotherapy improves loco-regional control. Despite these obvious advantages, protracted radiotherapy schedules and fear for acute and long-term toxicity invoke a reluctance, especially in low risk and older patients. Together with new insights in the radio-sensitivity of breast cancer, a solution to this problem has been sought in accelerating to schedules consisting of five or less high-dose fractions. Initially, these high-doses were limited to partial breast target volumes, limiting the advantages of acceleration to the more favourable risk groups [2].

Extending acceleration to all candidates for adjuvant breast radiotherapy, including indications for simultaneously integrated boost or lymph node irradiation, was the subject of the HAI-5 trial (Highly Accelerated Irradiation in five fractions), a feasibility trial limited to women over 65 years, applying a five-fraction schedule over two weeks for thoracic or whole breast irradiation and allowing simultaneously integrated boost (SIB) or lymph node irradiation (LNI) if indicated according to our in-house protocol. First data on acute toxicity have been reported and demonstrated feasibility with grade 2 dermatitis limited to 14.8% after breast-conserving surgery and 0% after mastectomy [3]. To compare these results with the actual gold standard of hypofractionation in fifteen fractions (HF15), we performed a matched case analysis.

Selection of matching criteria was based on a literature analysis, retaining breast volume [4] and presence of a boost [5], but not boost volume as most frequently reported factors related to radiation-induced acute toxicity. LNI and treatment position were also retained, as the first increases treatment volume and dose inhomogeneity, while the second has been demonstrated to have a protective effect.

2. Methodology

For this matched case analysis, only the subgroup of HAI-5 patients treated with breast conserving surgery (BCS) were retained for analysis [3]. Treatment schedule (HF5) consists of dose delivery every other day, administering five fractions of 5.76 Gy to the whole breast (WBI) with, if needed, a SIB of 5 × 6.5 or 6.9 Gy and LNI of 5 × 5.4 Gy.

This group is matched with patients from previous trials that applied HF15. Acute toxicity is evaluated during radiotherapy and two to four weeks after the last fraction, applying the Common Terminology Criteria for Adverse Events version 4.03 toxicity scoring system.

Each HF5 patient is matched with one control, selected by means of a propensity scoring method based on a combination of the exact method for LNI and inclusion of a boost, and a nearest neighbour method for breast volume and positioning (prone versus supine). To allow comparable age distribution, only controls of 65 years or over were retained, even though this impacted strongly the availability of ‘nearest neighbours’. The statistical software package R (version 3.0.1) is used for matching. In case of missing breast volumes, these data are estimated through a linear regression model in function of clinical target volume (CTV) of the breast.

The primary endpoint of our study is clinically relevant dermatitis, which is defined as a ≥ grade 2 dermatitis according to the Common Terminology Criteria for Adverse Events (CTCAE) scale. Secondary endpoints are desquamation, pain, pruritis and edema. Statistical difference of endpoints between the two schedules is evaluated with a paired Mc Nemar test, with rejection of the null-hypothesis if a significance
of \( p < 0.05 \) is reached. As we perform a double-sided testing, the experimental treatment is evaluated on being better or worse than standard HF15. SPSS 25 and statistical software package R are used for comparison of toxicity scores.

3. Results

Ninety-five patients were included in the HF5 trial, of whom 71 underwent WBI. Ten WBI patients were excluded for analysis because of age incompatibility, missing data in toxicity parameters or matching not possible. For matching, 422 controls treated with HF15 were available. Only the 130 controls of 65 years or over were retained. For each HF5 patient, an exact match based on target volume and boost could be found. Regarding treatment position, propensity scoring resulted in four HF5 patients treated in prone position, to be matched with four HF15 controls treated in supine position. Mean breast volume of the four HF5 patients treated in prone position, to be matched with four HF15 controls treated in supine position. Mean breast volume of the HF5 group was slightly lower, without differing significantly from the control group. Mean ages in HF5 and HF15 groups were respectively 73.6 and 70.5 years (\( p = 0.001 \)).

Acute toxicity was for all parameters lower for the HF5 group, but statistical significance was only reached for breast edema (Table 1, Fig. 1).

4. Discussion

In adjuvant breast radiotherapy, acute toxicity is related to late fibrosis and telangiectasia. This parameter seems a relevant substitute for late aesthetic outcome. Severe moist desquamation may result in treatment interruption or premature cessation, hence compromising the benefit of radiotherapy. Such experiences may lead to anxiety and thus induce a reluctance to radiotherapy. The FAST and FAST Forward trials, two randomized trials on “Radiation Therapy in Treating Women With Localized Breast Cancer", brought evidence that acceleration to five fractions is safe for early stage breast cancer [6]. These trials did not administer a boost nor LNI. In the French trial, boost and LNI indication were included, but with delivery of one fraction per week and with the boost delivered in one or two sequential fractions. The HAL-5 feasibility trial was intended to explore if the indication for a convenient five-fraction schedule over two weeks may safely be extended to more advanced stages, requiring a SIB and/or LNI. Moist desquamation was rare and only observed in case of boost administration. Although this is a retrospective analysis, targets and treatment techniques are similar between patient groups with matching correcting for target volume, boost, treatment position and breast volume. Toxicity results show no difference in acute toxicity between the two schedules, except for edema, which occurs significantly less in the HF5-schedule. Although rates of dermatitis and desquamation were halved and pruritus reduced with 30%, significance was not reached, due to underpowering. Homogeneous age groups were preferred to avoid all potential bias. The same age limit of 65 years or over was imposed for the matches. In most trials, older patients are underrepresented. This is reflected in the different age distribution between the two groups, where a statistically significant difference of three years in mean age is found between the HF5 and HF15 groups. As age has not been found a predictor for acute toxicity, this difference was accepted.

Omission of radiotherapy impairs breast cancer specific survival results [7]. Utilization of radiotherapy in older age groups remains too low, even in a country with easy access to radiotherapy [8]. Obstacles to radiotherapy may lead to omission of this treatment or to substitution by intra-operative irradiation techniques. Whereas the latter may improve results to some extent, a large group of more advanced stages remains either unaddressed or undertreated. Recurrence risk is also defined by histological cancer type. In very favourable subgroups omission of radiotherapy may not result in increased mortality, although it comes at the cost of higher recurrence rates [9]. In case of negative hormone receptors, patients over 80 years are more likely to die from breast cancer then from cardiovascular disease, while at the same time this age group receives less frequently radiotherapy. Combining adequate treatment with low toxicity and limited logistic burden may help to decrease a potential reluctance to radiotherapy in the older patient, thus aligning treatment choices with guidelines [10].

Another advantage of a HF5 over two weeks may rely in the shorter overall treatment time with higher tumoricidal effect, thus permitting reduction of the total dose. This may result in lower early and late toxicity. Three-year results of the FAST Forward trial seem to support this.

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<th>Table 1 Characteristics and acute toxicity.</th>
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HF5: hypofractionation in 5 fractions, HF15: hypofractionation in 15 fractions.

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hypothesis. In order to avoid the risk of time intervals lower than twelve hours between two fractions, we opted for a delivery every other day, guaranteeing thus at least 24 h normal tissue cell repair between two fractions. Lastly, when overall irradiation time shortens, this may allow a shift of radiotherapy to pre-chemotherapy or even pre-operative setting.

This matched-case analysis comes with some limitations. As the HAI-5 was only a feasibility trial, the number of patients was kept low on purpose. For validation, two randomized controlled trials and one patient preference trial, each comparing HF15 with HF5 are currently accruing. Due to higher age in the HAI-5 trial, compliance to follow up is a challenge, mainly because of impaired mobility, but also age-related morbidity and mortality. This may potentially compromise long-term follow-up of toxicity.

In conclusion, HF5 for early or loco-regionally advanced stage breast cancer is safe in terms of acute toxicity. In view of recommendations for treatment of breast cancer in older patients, short radiotherapy schedules may constitute a more convenient alternative to hypofractionation, thus addressing the challenge to improve adherence to guidelines in the older population.

Conflict of Interest

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Disclosure

None of the authors has any disclosures to report.

Author Contributions

Hans Van Hulle: Conception and design, data analysis, statistical analysis, writing of manuscript.
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Pieter Deseyne: Patient accrual, data analysis, review of manuscript.
Yolande Lievens: Review of manuscript.
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Liv Veldeman: Study coordination, patient accrual, data analysis, revision of manuscript.
Chris Monten: Study coordination, patient accrual, data analysis, writing of manuscript.

References